In This Issue

Cell

Getting to the Heart of Hypertrophy

PAGE 453

Cardiac muscle cells respond to various stress signals by hypertrophic growth. Hypertrophy can have initial beneficial effects on cardiac function but when prolonged is a major predictor of heart failure. Previous work has shown that class II histone deacetylases (HDACs) inhibit cardiac growth. *Song et al.* now identify a family of calmodulin binding transcription activators (CAMTAs) that act as regulators of hypertrophic growth. They show that class II HDACs inhibit the activity CAMTAs. However, in response to stress signals, the deacetylases are exported from the nucleus, allowing CAMTAs to activate hypertrophy. These results provide further insight into the mechanism underlying stress-induced cardiac hypertrophy.

A Sexy Function for a Histone Demethylase

PAGE 483

Histone methylation plays important roles in regulating chromatin dynamics and transcription and was thought to be an irreversible modification until recently. *Yamane et al.* use a biochemical assay coupled with chromatography to identify the histone demethylase JHDM2A that specifically catalyzes demethylation of mono- and dimethylated lysine 9 of histone H3. JHDM2A interacts with androgen receptor in a hormone-dependent manner and functions as a coactivator for androgen receptor. Thus, this work links the histone demethylase JHDM2A to hormone-dependent transcriptional activation.

A Histone Tri-Demethylase

PAGE 467

Modifications of histones, including methylation and acetylation, regulate chromatin biology and the epigenetic state of the cell. Although di-methylation of lysines on histones has been shown to be reversible by specific demethylases, it has been unclear whether tri-methylation is also reversible. Here, *Whetstine et al.* show that a family of four proteins (JMJD2A-D), containing the JmjC metalloenzyme domain, act as histone tri-demethylases by removing methyl groups from specific tri-methylated lysines in histones. Furthermore, inhibition of the only *C. elegans* JMJD2 homolog triggered p53-dependent germline apoptosis, suggesting an important in vivo role for histone demethylases.

CLOCK Has a HAT

PAGE 497

The circadian clock is based on transcriptional regulatory loops that generate time-specific activation of gene expression. Whether physiological circadian signals lead to changes at the level of chromatin remodeling remains an open question. Now, *Doi* and colleagues reveal that CLOCK, a transcription factor central to the circadian pacemaker, has enzymatic activity and directly acetylates histones. The HAT function of CLOCK is essential for rhythmic expression of target genes, suggesting that chromatin remodeling contributes to the core mechanism of the circadian clock.

Helping Wingless Fly

PAGE 509 and PAGE 523

Wnt proteins are secreted factors that control multiple biological processes in development and disease. While the Wnt signalling pathway is well understood, little is known about mechanism of Wnt secretion from cells. Two groups have now identified a seven-pass transmembrane protein required for the secretion of Wingless, the *Drosophila* Wnt homolog. *Bänziger et al.* and *Bartscherer et al.* find that the protein, Wntlesss/Evenness interrupted (Wls/Evi), is highly conserved from worms to mammals. The groups suggest that Wls/Evi is an ancient partner of Wnt proteins required for their release into the extracellular milieu.

Separating Flagella Form and Function

PAGE 549

Primary cilia are widely used for signal transduction during development and homeostasis. Cilia are assembled and maintained by intraflagellar transport (IFT) proteins. *Wang et al.* have dissected the role of IFT in signaling within the flagella, the structural and functional counterparts of cilia in the green alga *Chlamydomonas*. The authors demonstrate that IFT proteins are used not only for assembling and disassembling the structural components of flagella but independently also for organizing a signaling pathway that is initiated by flagellar adhesion during fertilization. The results suggest that the role of the IFT machinery in the assembly of cilia and flagella is separable from its role in signaling.

Riches in the Polarity Proteome

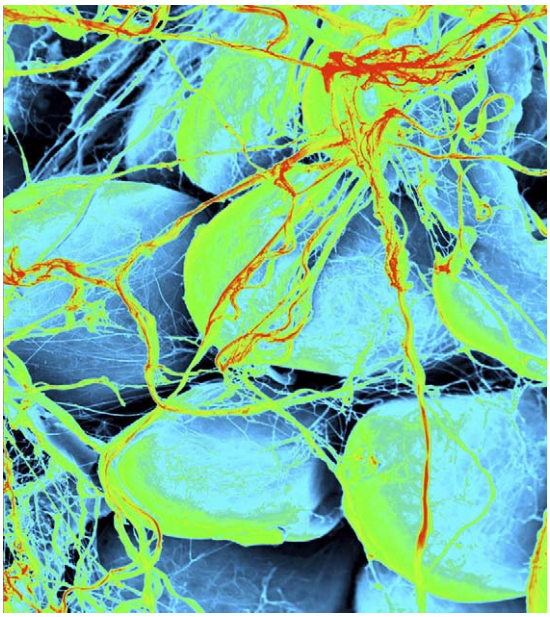
PAGE 535

Maintenance of epithelial cell polarity is important for proper cell morphology and in the formation of contacts, or tight junctions, with neighboring cells. Cdc42, a Rho GTPase family member, participates in a wide variety of cellular processes, including cell polarity, but its precise role in this process wasn't well established. Here *Wells et al.* use a proteomics approach to probe Cdc42 function at tight junctions by studying its local regulators. The authors identify a network of protein interactions that link a set of known polarity proteins with the Cdc42-specific RhoGAP protein Rich1, through the scaffolding protein Angiomotin. These results provide important insights into the protein interaction networks dictating epithelial polarity.

Understanding Opportunistic Infections in Plants

PAGE 563

Exposure of plants to nonpathogenic bacteria triggers an immune response that depends on the recognition of microbe-associated molecular patterns (MAMPs), but the downstream signalling pathways are not well understood. *He et al.* now find that the same immune response is also activated by pathogenic bacteria, but only transiently. They find that two pathogenic virulence factors, AvrPto and AvrPtoB, specifically shut down this basic immune response by inhibiting a MAMP-triggered MAPK pathway. *Arabidopsis* plants infected with AvrPto and AvrPtoB are deficient in MAMP-mediated immunity and become susceptible to opportunistic infections by normally nonpathogenic bacteria. These results thus provide insight into the mechanisms that make plants susceptible to opportunistic bacterial infections.



Sculpting Fat in 3D

PAGE 577

White adipose tissue (WAT) serves as the major energy depot in the body by storing fat within lipid-laden adipocytes. As fat cell precursors differentiate, complex transcriptional programs are engaged to support their hypertrophic growth into mature adipocytes. *Chun et al.* show that WAT development displays an unexpected requirement for a membrane-anchored collagenase, termed MT1-MMP, that serves to control adipocyte differentiation and growth by proteolytically sculpting the surrounding three-dimensional extracellular matrix. These results identify MT1-MMP as a novel adipogenic cofactor that regulates the dynamic adipocyte-extracellular matrix interactions critical to WAT development.

A New Prop for β-Catenin

PAGE 593

The Wnt/β-catenin signaling pathway plays an essential role in cell-fate determination in both development and disease, working generally through Tcf/Lef transcription factors. *Olson et al.* explore the transcriptional mechanism underlying β-catenin control of cell lineage determination in pituitary organogenesis. In this context they find that instead of the canonical Lef/Tcfs, a tissue-specific homeodomain factor, Prop1, is the essential DNA binding transcription factor that recruits β-catenin and mediates the actions of the Wnt/β-catenin pathway. These data demonstrate a Lef/Tcf-independent mechanism of Wnt signaling and suggest that tissue-specific homeodomain transcription factors partnering with β-catenin may be a widely used strategy in mammalian organogenesis.

Dscam: The 38,000 Isoform Question

PAGE 607

The complexity of synaptic connections in the nervous system requires a molecular recognition mechanism of exquisite specificity. It remains a puzzling question how a relatively small amount of genetic information can specify millions of synaptic contacts. The *Drosophila* Dscam gene generates over 38,000 receptor isoforms via alternative splicing. In this paper, *Chen et al.* analyzed the targeting of single axon branches within the CNS and found that flies expressing a reduced subset of 22,000 Dscam isoforms show specific targeting errors. Flies that lacked different subsets of isoforms exhibited distinguishable defects. The results suggest that tens of thousands of structurally different receptors specify connectivity in a *Drosophila* sensory circuit.